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AMENDMENTS TO THE CLAIMS

Please amend claims 1, 2, 3, 16, 25, 29, 34, 47 and 66 as indicated below.

This listing of claims below will replace all prior versions, and listings, of claims in the application:

Listing of Claims

1. (Currently Amended) A method of treating a mammal which has impaired glucose tolerance or early stage diabetes mellitus, comprising orally administering a therapeutically effective dose of a pharmaceutical formulation comprising insulin and an effective amount of a pharmaceutically acceptable delivery agent ~~comprising~~ 4-CNAB which facilitates absorption of said insulin from the gastrointestinal tract of said mammals at or shortly before bedtime.

2. (Currently Amended) The method of claim 1 wherein the treating comprises ~~preventing~~ substantially reducing the incidence of beta cell death or dysfunction.

3. (Currently Amended) The method of claim 1 wherein the treating comprises long term ~~protection from~~ reduction in the incidence of developing overt diabetes.

4. (Previously Presented) The method of claim 1 wherein the treating comprises delaying the onset of overt or insulin dependent diabetes.

5. (Previously Presented) The method of claim 1, wherein the mammal is a rodent, dog, cat, sheep, pig, cow, horse or human.

6. (Original) The method of claim 5, wherein the mammal is a human.

7. (Previously Presented) The method of claim 1, wherein the oral pharmaceutical formulation is administered on a chronic basis.

8. (Previously Presented) The method of claim 1, wherein the oral pharmaceutical formulation is administered nightly for at least two weeks.

9. (Original) The method of claim 5, which provides a lowering of morning or fasting insulin levels of at least about 20%.

10. (Original) The method of claim 5, which achieves a therapeutically effective reduction in blood glucose after oral administration to a human diabetic patient, and which provides a ratio of portal vein to peripheral blood insulin concentration from about 2.5:1 to about 6:1.

11. (Previously Presented) The method of claim 5, wherein the dose of the pharmaceutical composition is administered through a dosage form that is solid.

12. (Previously Presented) The method of claim 1, wherein the dose of insulin contained in the dosage form is from about 50 Units to about 600 Units.

13. (Previously Presented) The method of claim 1, wherein the dose of unmodified insulin is from about 100 Units to about 400 Units insulin.

14. (Previously Presented) The method of claim 1, wherein the dose of unmodified insulin is from about 150 Units to about 300 Units.

15. (Previously Presented) The method of claim 1, wherein the dosage form(s) begin delivering insulin into the portal circulation (via absorption through the mucosa of the gastrointestinal tract) to achieve peak levels within about 30 minutes or less.

16. (Currently Amended) A method of treating mammals having impaired glucose tolerance or early stage diabetes mellitus, comprising,

orally administering insulin and an effective amount of a pharmaceutically acceptable delivery agent ~~comprising~~ 4-CNAB which facilitates absorption of said insulin from the gastrointestinal tract of said mammals at or shortly before bedtime to mammals having impaired glucose tolerance or early stage diabetes mellitus such that a statistically significant decrease in C-peptide levels from a mean baseline level is achieved in said mammals when said C-peptide level is measured about 8 hours after said oral administration of insulin.

17. (Original) The method of claim 16, wherein said C-peptide levels when measured are decreased by a mean of about 24%.

18. (Previously Presented) The method of claim 16, wherein plasma insulin levels are reduced by a statistically significant degree from baseline when measured about 8 hours after said oral administration of insulin.

19. (Original) The method of claim 18, wherein said plasma insulin levels are reduced by a mean of about 33% from baseline when measured about 8 hours after said oral administration of insulin.

20. (Previously Presented) The method of claim 16, wherein blood glucose levels are reduced by a statistically insignificant degree from baseline when measured about 8 hours after said oral administration of insulin.

21. (Original) The method of claim 20, wherein said blood glucose levels are reduced by a mean of about 6% from baseline when measured about 8 hours after said oral administration of insulin.

22. (Previously Presented) The method of claim 16, wherein said oral administration of insulin comprises a dose of from about 200 to about 400 units of insulin.

23. (Canceled)

24. (Previously Presented) The method of claim 16, wherein said pharmaceutically acceptable delivery agent comprises about 300 mg 4-CNAB.

25. (Currently Amended) A method of treating mammals having impaired glucose tolerance or early stage diabetes mellitus, comprising orally administering an unmodified insulin and an effective amount of a pharmaceutically acceptable delivery agent comprising 4-CNAB which facilitates absorption of said insulin from the gastrointestinal tract at or shortly before bedtime to mammals having impaired glucose tolerance or early stage diabetes mellitus such that a statistically significant decrease in C-peptide levels from a mean baseline level is achieved in

said mammals when said C-peptide level is measured about 8 hours after said oral administration of insulin.

26. (Canceled)

27. (Previously Presented) The method of claim 1, wherein said oral administration provides an insulin t_{max} at a time point from about 0.1 to about 1.5 hours after said oral administration, such that a statistically significant decrease in C-peptide levels from baseline is achieved in said mammal when said C-peptide level is measured about 8 hours after said oral administration of insulin.

28. (Previously Presented) The method of claim 1, wherein plasma insulin levels are reduced by a statistically significant degree from baseline when measured about 8 hours after said oral administration of insulin.

29. (Currently Amended) The method of claim 1 wherein the treating comprises prophylactically ~~sparing~~ reducing beta cell function.

30-32. (Canceled)

33. (Previously Presented) The method of claim 1, wherein said pharmaceutically acceptable delivery agent comprises about 300 mg 4-CNAB.

34. (Currently Amended) A method of treating a mammal which has impaired glucose tolerance or early stage diabetes mellitus, comprising orally administering a therapeutically effective dose of a pharmaceutical formulation comprising an unmodified insulin and an effective amount of a pharmaceutically acceptable delivery agent 4-CNAB which facilitates absorption of said insulin from the gastrointestinal tract of said mammal at or shortly before bedtime.

35. (Previously Presented) The method of claim 1, wherein C-peptide levels of said mammal are decreased by a mean of about 24% when measured about 8 hours after said oral administration of insulin.

36. (Previously Presented) The method of claim 1, wherein plasma insulin levels of said mammal are reduced by a mean of about 33% when measured about 8 hours after said oral administration of insulin.

37. (Previously Presented) The method of claim 1, wherein blood glucose levels of said mammal are reduced by a mean of about 6% when measured about 8 hours after said oral administration of insulin.

38. (Previously Presented) The method of claim 16, wherein said mammal is a human.

39. (Canceled)

40. (Previously Presented) The method of claim 25, wherein said C-peptide levels when measured are decreased by a mean of about 24%.

41. (Previously Presented) The method of claim 25, wherein plasma insulin levels are reduced by a statistically significant degree from baseline when measured about 8 hours after said oral administration of insulin.

42. (Previously Presented) The method of claim 41, wherein said plasma insulin levels are reduced by a mean of about 33% from baseline when measured about 8 hours after said oral administration of insulin.

43. (Previously Presented) The method of claim 25, wherein blood glucose levels are reduced by a statistically insignificant degree from baseline when measured about 8 hours after said oral administration of insulin.

44. (Previously Presented) The method of claim 43, wherein said blood glucose levels are reduced by a mean of about 6% from baseline when measured about 8 hours after said oral administration of insulin.

45. (Previously Presented) The method of claim 25, wherein said oral administration of insulin comprises a dose of from about 200 to about 400 units of insulin.

46. (Previously Presented) The method of claim 25, wherein said oral administration of insulin comprises a dose of from about 100 to about 400 units of insulin and an effective amount of a pharmaceutically acceptable delivery agent which facilitates absorption of said insulin from the gastrointestinal tract.

47. (Currently Amended) The method of claim 46, wherein said pharmaceutically acceptable delivery agent ~~comprises~~ is 4-CNAB.

48. (Previously Presented) The method of claim 25, wherein said pharmaceutically acceptable delivery agent comprises about 300 mg 4-CNAB.

49. (Previously Presented) The method of claim 25, wherein the mammal is a human.

50. (Previously Presented) The method of claim 34, wherein the mammal is a human.

51. (Previously Presented) The method of claim 34, wherein the oral pharmaceutical formulation is administered on a chronic basis.

52. (Previously Presented) The method of claim 34, wherein the oral pharmaceutical formulation is administered nightly for at least two weeks.

53. (Previously Presented) The method of claim 34, which provides a lowering of morning or fasting insulin levels of at least about 20%.

54. (Previously Presented) The method of claim 34, which achieves a therapeutically effective reduction in blood glucose after oral administration to a human diabetic patient, and which provides a ratio of portal vein to peripheral blood insulin concentration from about 2.5:1 to about 6:1.

55. (Previously Presented) The method of claim 34, wherein the dose of the pharmaceutical composition is administered through a dosage form that is solid.

56. (Previously Presented) The method of claim 34, wherein the dose of insulin contained in the dosage form is from about 50 Units to about 600 Units.

57. (Previously Presented) The method of claim 34, wherein the dose of unmodified insulin is from about 100 Units to about 400 Units insulin.

58. (Previously Presented) The method of claim 34, wherein the dose of unmodified insulin is from about 150 Units to about 300 Units.

59. (Previously Presented) The method of claim 34, wherein the dosage form(s) begin delivering insulin into the portal circulation (via absorption through the mucosa of the gastrointestinal tract) to achieve peak levels within about 30 minutes or less.

60. (Previously Presented) The method of claim 34, wherein said oral administration provides an insulin t_{max} at a time point from about 0.1 to about 1.5 hours after said oral administration, such that a statistically significant decrease in C-peptide levels from baseline is achieved in said mammal when said C-peptide level is measured about 8 hours after said oral administration of insulin.

61. (Previously Presented) The method of claim 34, wherein plasma insulin levels are reduced by a statistically significant degree from baseline when measured about 8 hours after said oral administration of insulin.

62. (Previously Presented) The method of claim 34, wherein C-peptide levels of said mammal are decreased by a mean of about 24% when measured about 8 hours after said oral administration of insulin.

63. (Previously Presented) The method of claim 34, wherein plasma insulin levels of said mammal are reduced by a mean of about 33% when measured about 8 hours after said oral administration of insulin.

64. (Previously Presented) The method of claim 34, wherein blood glucose levels of said mammal are reduced by a mean of about 6% when measured about 8 hours after said oral administration of insulin.

65. (Previously Presented) The method of claim 34, wherein said dose of pharmaceutical formulation comprises from about 200 to about 400 units of insulin and further comprises an effective amount of a pharmaceutically acceptable delivery agent which facilitates absorption of said insulin from the gastrointestinal tract of said mammals.

66. (Currently Amended) The method of claim 65, wherein said pharmaceutically acceptable delivery agent ~~comprises~~ 4-CNAB.

67. (Previously Presented) The method of claim 66, wherein said pharmaceutically acceptable delivery agent comprises about 300 mg 4-CNAB.